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Adaptive Radiation Therapy for Intact Thymoma: An Illustrative Report

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Abstract. *Background/Aim: Adaptive radiation therapy (ART) is a technique capable of reducing radiation dose to normal tissue without compromising local control. For potentially resectable thymoma, induction therapy is standard of care. Because large disease volume is common in this context, ART has been suggested to reduce toxicity from induction chemoradiation. This has not been previously illustrated in the literature. Case Report: A 38-year-old man with initially unresectable thymoma was treated with induction chemoradiation including cisplatin and etoposide. He received 45 Gy in 25 fractions and ART was utilized to shrink the radiotherapy field for the final 10 fractions. Results: Thymectomy showed Masaoka stage III disease with negative margins. He experienced no treatment-related toxicity and has no evidence of disease 8 years after diagnosis. Conclusion: Induction chemoradiotherapy with ART appears to be feasible, safe, and efficacious for locally advanced intact thymoma.*

Thymoma is the most common primary mediastinal tumor. The WHO histologic classification system categorizes these tumors and offers prognostic value (1-2). The Masaoka staging system is used to determine management and prognosis (3). Standard of care is surgery, with adjuvant radiation or chemoradiation for locally advanced disease or positive margins (4). In patients with initially unresectable disease, induction therapy is utilized to shrink the tumor. Overall local recurrence is around 11% at 10 years (2).

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Key Words: Adaptive radiation therapy, WHO Type B2 thymoma, induction chemoradiation, radiosensitive malignancy, intact thymoma.

Because of the mediastinal location of thymomas, radiotherapy can cause significant toxicity including pericardial effusions, radiation pneumonitis, pulmonary fibrosis, and esophageal stricture (5). To allow for more accurate radiation delivery and thus reduce toxicity, technical advances such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and adaptive radiotherapy (ART) have been developed (5). The goal of ART is to reduce radiation dose to normal tissue without compromising local control. While ART does not have a major role in the post-operative setting because the target includes potential subclinical disease in the tumor bed, it can potentially have a major role in intact thymoma. We present the first published report illustrating the use of ART in the induction setting for thymoma.

Case Report

A 38-year-old man with no past medical history presented to the emergency department with chest discomfort, fevers, and night sweats after running a marathon. A CT scan revealed a 9×8.5 cm right anterior mediastinal mass contiguous with a 9×6.7 cm right infrahilar mass. On PET/CT (Figure 1A), the mass had a standardized uptake value (SUV) of 6.5 and there was no evidence of metastatic disease. Biopsy showed WHO type B2 lymphocyte rich thymoma (Figure 2). On cardiac magnetic resonance imaging (MRI) the mass was 950 cc without pericardial infiltration or compression of cardiac structures.

The patient was treated with induction chemoradiotherapy followed by surgery. Radiotherapy planning utilized a 4DCT to generate an internal target volume (ITV). A 1 cm planning

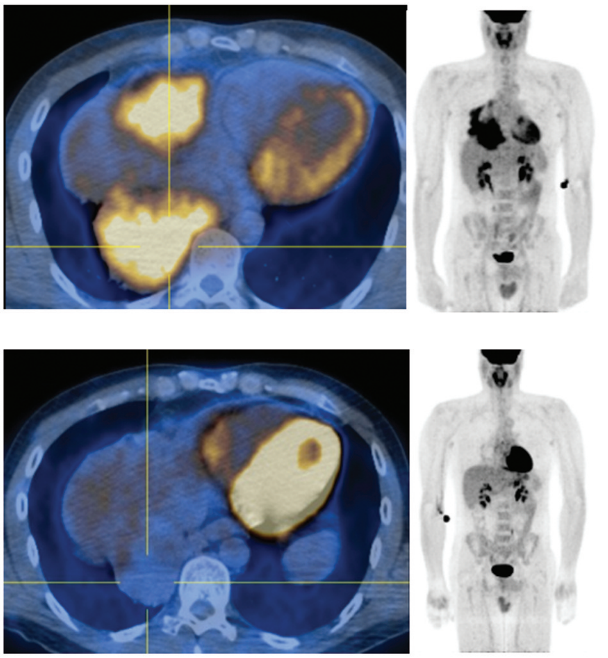

Figure 1. *Positron emission tomography-computed tomography (PET/CT) scan. Top: Before induction chemoradiation. Bottom: After induction chemoradiation.*

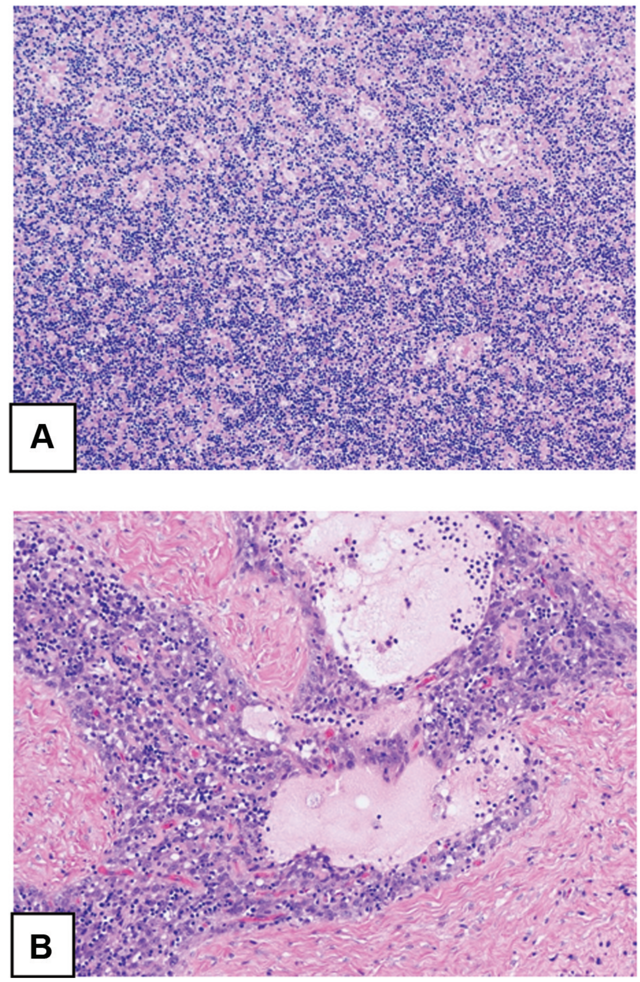

Figure 2. *Hematoxylin and Eosin stains. (A) Tumor with mixed epithelial and lymphocyte rich areas (magnification 300×). (B) Tumor with more epitheliod clusters with a decreased amount of lymphocytes (magnification 300×).*

Table I. *Comparison of PTV and right lung volumes on the initial plan and the new plan.*

Structure	Initial volume (cc)	New volume (cc)	Percent change
PTV	2,422	1,830	–24%
Right lung	1,264	1,967	+56%

PTV: Planning target volume; cc: cubic centimeter.

target volume (PTV) margin was placed around the ITV and this volume was treated with IMRT to 45 Gy in 25 fractions over the span of five weeks using helical tomotherapy. Chemotherapy consisted of cisplatin 50 mg/m^2 (administered on days 1, 8, 29, and 36) and etoposide 50 mg/m^2 (administered on days 1-5 and 29-33).

IGRT was utilized *via* daily megavoltage computed tomography (MVCT) scans before each treatment to allow for correction of interfractional changes in tumor positioning. By fraction 5, MVCT scans demonstrated a significant decrease in tumor size (Figure 3). Based on this marked radiographic response, it was determined that the patient would likely benefit from ART. On the day of fraction 8, a new 4DCT simulation was performed to create a new treatment plan for ART. A decrease in tumor size and re-expansion of the right lung are evident on comparison of the two 4DCT average intensity projection scans (Figure 4). The initial and new volumes of the PTV and normal right lung are compared in Table I. Due to the time required for re-planning, the new treatment plan was not utilized until fraction 16.

After the patient completed induction therapy, a repeat PET/CT (Figure 1B) demonstrated significant reduction in both mediastinal and infrahilar components of the mass. The majority of the remaining mass demonstrated no tracer uptake. The patient then underwent thymectomy. On microscopic evaluation, the majority of the tumor consisted of large atypical epithelial cells admixed with lymphocytes, consistent with a WHO type B2 thymoma. Other areas showed more epithelioid clusters and less lymphocytes,

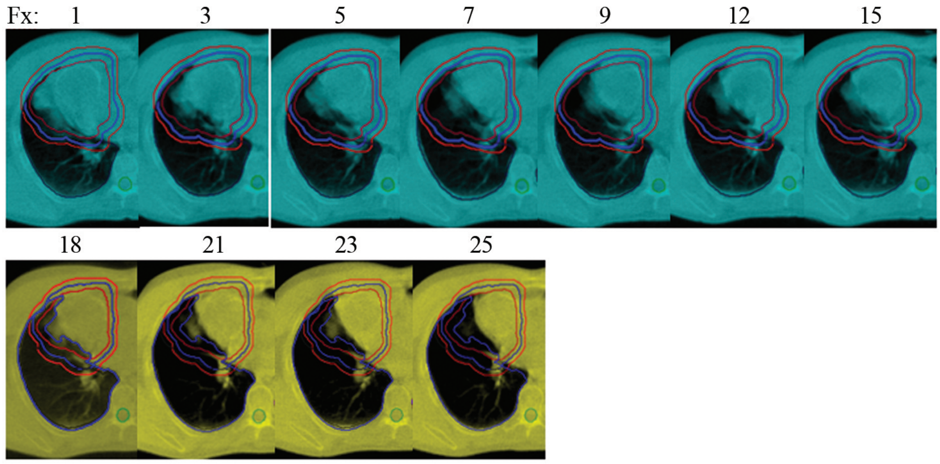

Figure 3. *Megavoltage computed tomography (MVCT) scans at the time of specific fraction (fx) delivery. The contours in the top row show the initial internal target volume (ITV), clinical target volume (CTV), and planning target volume (PTV). Those in the second row show the new ITV, CTV, and PTV.*

Table II. *Calculated lung dosimetry for 3 scenarios: 1) the hypothetical scenario without ART; 2) the actual treatment delivered with ART starting on fraction 16; 3) the hypothetical scenario with ART starting on the same day of repeat simulation (fraction 8).*

Organ	Metric	No ART	ART on Fraction 16 (Actual)	ART on Fraction 8
Both lungs	V_{10} (%)	67.6	62.8	59.7
	V_{20} (%)	30.6	26.2	23.4
	V_{30} (%)	25.1	15	8.5
	V_{40} (%)	8.6	6.4	5
	V_{50} (%)	0.7	0.3	0
	Mean dose (Gy)	17	15.4	14.4

ART: Adaptive radiation therapy; V_{10}: volume receiving 10% of the dose; V_{20}: volume receiving 20% of the dose; V_{30}: volume receiving 30% of the dose; V_{40}: volume receiving 40% of the dose; V_{50}: volume receiving 50% of the dose; Gy: gray.

consistent with a WHO type B3 thymoma. Chemoradiation changes were seen including extensive tumor necrosis and calcification. Surgical margins were negative. The tumor was characterized as Masaoka stage III. The patient recovered well from surgery and received two more cycles of chemotherapy. He tolerated the adjuvant chemotherapy and currently has no evidence of disease 8 years after the initial diagnosis. He has no significant side effects from treatment.

Discussion

The concept of ART was first formally introduced by Yan *et al*. in 1997 (6). A recent review article by Badley *et al*. in 2019 provides an overview of current ART strategies (7). The overall objective of this technological advancement is to improve the quality of a patient's treatment by maintaining prescribed dose to the target while reducing dose to healthy tissue (8). Because re-planning radiotherapy treatment takes time, ART is only worthwhile in tumors that have significant shrinkage early in the treatment course. For this reason, ART has predominantly been utilized for head and neck and lung tumors (7, 9-10). A recent review of 29 articles regarding ART for head and neck cancer suggested that ART may decrease toxicity and improve local control for locally advanced head and neck cancer (9). A recent phase 2 clinical trial evaluated ART for non-small-cell lung cancer and demonstrated favorable local-regional tumor control (10). While many types of malignancies shrink very slowly and thus are not amenable to ART, thymoma is known to be a radiosensitive tumor (11). Although ART is certainly being used for thymoma at many institutions, there are no prior publications illustrating the impact of ART for thymoma.

While induction therapy is standard of care for patients with initially unresectable thymoma, induction chemotherapy is more common than induction chemoradiation because these tumors are often very large and thus would require large

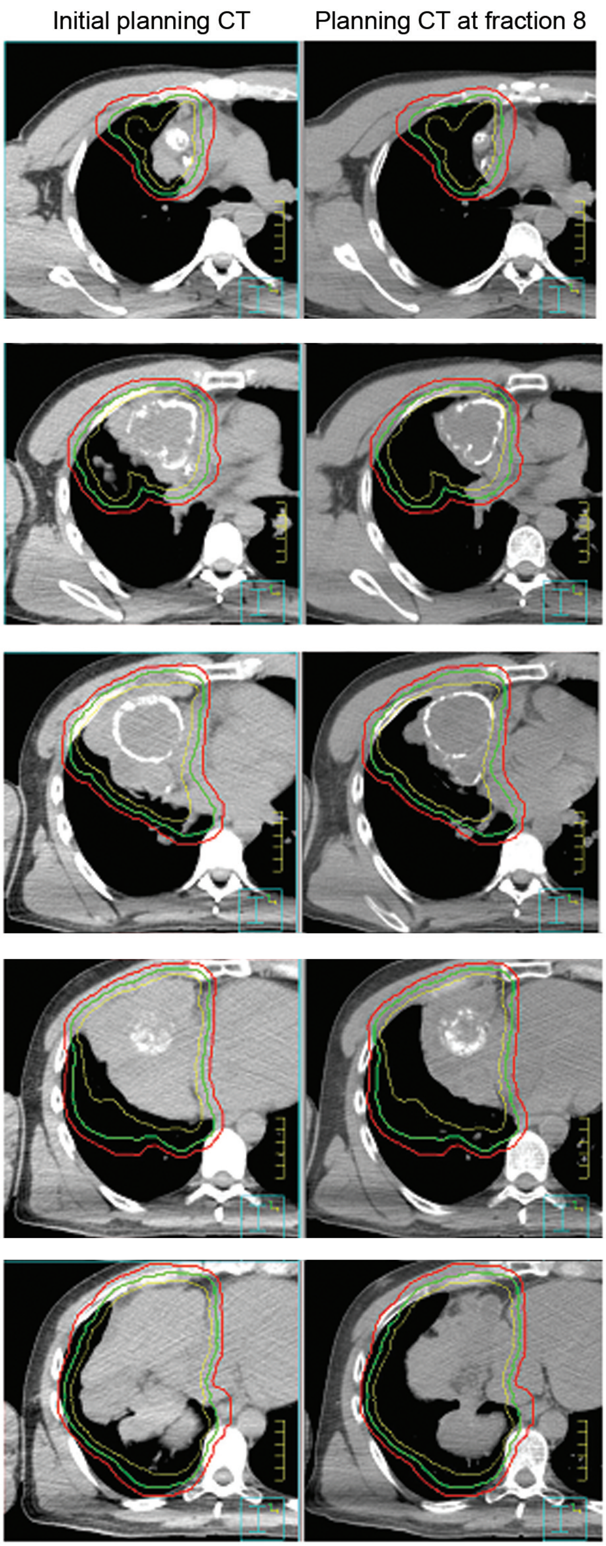

Figure 4. *Planning computed tomography (CT). Initial (left column) and new (right column) 4DCT average intensity projection planning scans with initial internal target volume (ITV), initial clinical target volume (CTV), and initial planning target volume (PTV) drawn on both sets of scans for comparison.*

radiotherapy fields (4, 12). However, there are notable benefits of concurrent chemoradiation including the synergistic effects of combining chemotherapy with radiation and the increased ability to obtain an R0 resection (12). A retrospective review of 10 patients with locally advanced thymic tumors treated with induction chemoradiation consisting of cisplatin and etoposide resulted in 8 patients receiving an R0 resection and 2 patients receiving an R1 resection (12). Since large radiotherapy fields is the major disadvantage of induction chemoradiotherapy relative to induction chemotherapy, one method to obtain the benefits of induction chemoradiotherapy while minimizing the detrimental effects of large radiotherapy fields is the utilization of ART.

This patient had a very large tumor that showed significant radiographic response early in the chemoradiation course. Therefore, he was the ideal candidate for ART. Table II depicts the lung dosimetry for his case and compares it to both the hypothetical lung dosimetry had he not received ART and the hypothetical lung dosimetry if ART treatment could have been initiated the same day the adaptive 4DCT simulation was performed. This highlights not only the benefit of ART but also the added value of rapid re-planning.

The histological classification of his thymoma may be responsible for his rapid radiographic response to chemoradiation. While all thymomas are known to be radiosensitive, WHO type B2 thymoma has abundant immature T cells so theoretically it should be even more sensitive to chemoradiation (1). Unfortunately, due to the low incidence of thymoma in general, there are no published studies demonstrating different levels of radiosensitivity for different thymoma histologies.

The patient has done very well without any recurrence or treatment-related toxicity. Concurrent induction chemoradiotherapy with ART successfully down-staged the disease allowing for optimal surgical resection while minimizing the irradiation volume of normal tissues. Therefore, ART appears to be feasible, safe, and efficacious for locally advanced intact thymoma.

Conflicts of Interest

The Authors report no conflicts of interest.

Authors' Contributions

Neil Chevli: Data curation, validation, review & editing. Ross E. Bland: Data curation, original draft. Andrew M. Farach: Conceptualization, review & editing. Thomas Mathews: Data curation, review & editing. Ramiro Pino: Data curation, review & editing. Ekene I. Okoye: Conceptualization, review & editing. Shanda Blackmon: conceptualization, review & editing. E. Brian Butler: Conceptualization, investigation, review & editing. Bin S. Teh: Conceptualization, investigation, project administration, supervision, validation, review & editing.

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